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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,325	08/10/2001	Martin Gleave	UBC.P-020	8469

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/913,325	GLEAVE ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8-17 and 29-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,10,12-17,31,32,36,38-40 and 42* is/are rejected.

7)☒ Claim(s) *9,11,29,30,33-35,37,41 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Double Patenting

The provisional obviousness-type double patenting rejection over copending Application No. 09/967,726 is withdrawn in view of the terminal disclaimer filed in the '726 application.

Claim Rejections - 35 USC § 103

The rejection of record has been re-written in view of applicants' arguments to clarify the teachings found in the Bruchovsky reference.

Claims 6, 8, 10, 12-17, 31, 32, 36, 38-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchovsky et al. (Prostate Suppl. 1996, of record) in view of Monia et al. (US 5,563,255, of record), Baracchini et al. (US 5,801,154, of record), Sensibar et al. (Cancer Research 1995, of record), Kyprianou et al. (Int. J. Cancer 1997, of record) and Raghavan et al. (European Journal of Cancer 1997, of record).

The claimed invention is directed to methods of treating prostate cancer with a combination therapy comprising androgen withdrawal and an antisense oligonucleotide that inhibits expression of TRPM-2. The antisense oligonucleotide can be that

designated as SEQ ID NO: 5. In additional embodiments this combination therapy is further combined with a chemotherapeutic agent such as a taxane, an antisense oligonucleotide targeted to another anti-apoptotic protein such as Bcl-2, or both.

Bruchovsky et al. teach that progression of prostate tumors to an androgen independent state can be delayed by maintaining the tumor in a state susceptible to apoptosis. Such maintenance is accomplished by repeated cycles of androgen withdrawal and replacement. Bruchovsky et al. teach that in rats bearing a prostate tumor model such treatment resulted in an increased time period before androgen independence. These experiments demonstrated that cycles of androgen withdrawal and replacement reinduce the apoptotic potential of tumor cells. Similar treatments have been repeated in humans with prostate cancer (see figure 3 and discussion on page 16 under heading "Clinical"). Bruchovsky et al. suggest that intermittent androgen withdrawal therapy can be improved by increasing the number of cycles before androgen independence. Bruchovsky et al. further teach that the different localization of clusterin (another name for TRPM-2) in androgen-dependent and -independent tumor cells indicates deregulation of TRPM-2 expression is promoted by androgen ablation and that TRPM-2 may foster the generation of androgen-independent cells in an androgen depleted environment (see abstract and discussion on page 19 under heading "Clusterin"). On page 20 Bruchovsky et al. suggest a prostate cancer treatment that includes augmentation of intermittent therapy by administration of additional chemotherapeutic agents such as cytotoxic drugs, radiation or gene therapy. Bruchovsky et al. explicitly suggest anti-TRPM-2 or anti-Bcl-2 gene therapy in conjugation with androgen withdrawal/replacement; the legend of figure 9 suggests

"antisense TRPM-2" and "antisense Bcl-2" as an augmentative therapy. While Bruchovsky et al. teach that TRPM-2 and Bcl-2 antisense oligonucleotides are envisioned as gene therapy, they do not exemplify the use of such antisense oligonucleotides as gene therapy.

It was well recognized in the art at the time of invention that antisense inhibition of gene expression is a form of gene therapy and that antisense oligonucleotides can be readily prepared to any known gene. See for example, Monia et al., who teach at column 2, lines 1-36 that teach that numerous examples are known of use of antisense oligonucleotides as gene therapy and that it has been established by workers in the field that antisense oligonucleotides can be useful therapeutic instrumentalities and can be configured to be useful in treatment regimes for treatment of cells and animal subjects, especially humans. Monia et al. further teach at column 4, line 55 through column 8, line 60 how to target an antisense to a gene and how to modify the oligonucleotide in order to improve pharmacokinetic parameters important for therapeutic applications. Monia et al. teach in the examples the successful practice of general antisense design taught at columns 4-8 and provide a detailed blueprint for how to make and use inhibitory antisense oligonucleotides to target any known gene. At column 5 Monia et al. teach that oligonucleotides targeted to the translation initiation codon are preferred.

The teachings of Baracchini et al. parallel those of Monia, teaching at column 4 that oligonucleotides have recently become accepted as drugs for the treatment of disease states in animals and man. Antisense oligonucleotide therapeutic compositions capable of modulating expression of genes implicated in disease have been identified by workers in the field and efficacy has been demonstrated for several oligonucleotide

drugs. Baracchini et al. further teach at columns 6-8 targeting and modification to antisense oligonucleotides. At columns 9-10 Baracchini et al. teach that translation initiation and termination regions are preferred target regions for antisense oligonucleotides.

Sensibar et al. teach phosphorothioate antisense oligonucleotides fully complementary to a nucleic acid encoding Sulfated glycoprotein-2 (an alternative name for TRPM-2), including the translation initiation codon. This sequence is identical to that designated as SEQ ID NO: 5 in the instant application. When transfected into LNCaP cells (a human prostate cancer cell line), these antisense oligonucleotides resulted in a decline of SGP-2 synthesis, indicating that expression of SGP-2 was inhibited (see pages 2433-2435, section entitled "Effect of Antisense Oligonucleotides to SGP-2 on LNCaP Cells").

Kyprianou et al. teach that Bcl-2 expression in prostate tumors is associated with progression to androgen independence. Bcl-2 expression is also correlated with resistance to apoptosis. Kyprianou et al. suggest on page 347 that strategies that inhibit Bcl-2 such as antisense oligonucleotides may enhance prostate cancer treatment.

Raghavan et al. teach that cytotoxic chemotherapeutic agents including mitoxanthrone are commonly used in treatment of prostate cancer. Raghavan et al. further teach that taxanes such as paclitaxel have promising activity in combination therapies.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat prostate cancer with a combination of androgen withdrawal

and antisense oligonucleotides directed to TRPM-2, including SEQ ID NO: 5. Bruchovsky et al. provide a motivation to combine androgen withdrawal with TRPM-2 gene therapy; teaching androgen withdrawal is a routine treatment for prostate cancer, showing a link between tumor progression and inappropriate TRPM-2 expression, and explicitly suggesting a combination therapy that comprises antisense TRPM-2 and antisense Bcl-2. Based on the teachings of Monia et al. and Baracchini et al. and the legend for Figure 9 of Bruchovsky, one of ordinary skill in the art would readily recognize antisense oligonucleotides as the gene therapy suggested by Bruchovsky et al. Based on the demonstrated success at inhibiting TRPM-2 expression of the TRPM-2 antisense oligonucleotides taught by Sensibar et al., one would be motivated to use these antisense sequences. One of ordinary skill in the art would have had a reasonable expectation of success in combining androgen withdrawal and antisense oligonucleotide gene therapy because Bruchovsky et al. teach that androgen withdrawal is a routine treatment for prostate cancer and suggest it be combined with antisense gene therapy, the teachings of Monia et al. and Baracchini et al. demonstrate antisense oligonucleotides are recognized by those in the art as therapeutics and Sensibar et al. teach that antisense oligonucleotides such as that designated as SEQ ID NO: 5 successfully inhibit TRPM-2 gene expression.

It would have been further obvious to modify this combination prostate cancer treatment using chemotherapeutic agents and/or antisense oligonucleotides targeted to Bcl-2. Raghavan et al. provide a motivation to use chemotherapeutic agents to treat prostate cancer, teaching that these agents are commonly used and that paclitaxel has shown promise in combination with other treatments. Kyprianou et al. provide a

motivation to target Bcl-2 in prostate cancer, teaching a relationship between Bcl-2 expression and progression to androgen independence. Kyprianou et al. and Bruchovsky et al. both suggest that antisense oligonucleotides targeted to Bcl-2 may enhance other prostate cancer therapies. Additionally, Bruchovsky et al. provide a motivation to use either or both of chemotherapeutic agents and antisense oligonucleotides, suggesting a prostate cancer therapy comprising androgen withdrawal in combination with other therapeutic agents. One of ordinary skill in the art would have had a reasonable expectation of success in combining chemotherapeutic agents or Bcl-2 antisense oligonucleotide therapy with other prostate cancer therapies because Raghavan et al. teach that combination therapies comprising chemotherapeutic agents have been used for treatment of prostate cancer, Kyprianou et al. suggest that combination therapies comprising Bcl-2 inhibition would be useful and suggest use of antisense oligonucleotides to inhibit Bcl-2, and Sensibar et al. demonstrate that antisense oligonucleotides can be used to inhibit expression of a gene associated with prostate cancer.

Thus, the invention of claims 6, 8, 10, 12-17, 31, 32, 36, 38-40 and 42 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the rejection by arguing an understanding that antisense inhibition of gene expression would be therapeutic and would provide any discernable benefit to a patient is lacking. Applicants argue that the newly applied Monia and Baracchini references are generalized teachings with respect to gene therapy and do

not teach or suggest that TRPM-2 targeted antisense would be a type of antisense useful in gene therapy. This argument is not persuasive because the suggestion that antisense TRPM-2 targeted antisense would be a type of antisense useful in gene therapy can be found in the Bruchovsky reference. The rejection of record has been re-written to clarify the teachings of this reference. The teachings of the Monia and Baracchini references provide further evidence that those of ordinary skill in the art readily recognized at the time of invention that antisense oligonucleotides are therapeutic compounds.

Applicants further assert there is no reasonable expectation of success in combining the references, arguing that an understanding in the art as to the effect of TRPM-2 expression on apoptosis is an essential component to any conclusion of obviousness because if reduction of TRPM-2 actually prevented apoptosis, no therapeutic benefit would result from inhibiting this gene in combination with androgen withdrawal. Applicants further argue the benefits with regard to treatment of prostate cancer is a consequence of the reduction in TRPM-2 expression, but nothing in the art supports a conclusion that such a benefit was a necessary result of the change in expression.

This argument is not persuasive because regardless of whether the relationship between TRPM-2 expression and apoptosis was known, the prior art specifically suggests using the exact combination recited in the instant claims. While the outcome could not be absolutely predicted *a priori*, the Bruchovsky reference explicitly suggests combining androgen withdrawal and antisense inhibition of TRPM-2. An obviousness

rejection does not require absolute prediction of success, merely a reasonable expectation of success.

Applicants argue the previously submitted declaration evidence establishes the unexpected synergy that results from the combination of anti-TRPM-2 antisense and chemotherapy agents. Applicants' argument that the combination of TRPM-2 antisense and chemotherapeutic agents provides synergistic results is based on the observation that antisense alone had no effect on tumor volume. However, the evidence provided in the declaration appears to contradict the disclosure of the specification, which describes in the working examples that TRPM-2 antisense oligonucleotides significantly decrease tumor size in mice bearing PC-3 tumors. Clarification is requested with regard to the different results observed in the experiments described in the specification and in the declaration.

Applicants additionally point out that the teaching of Kyprianou of the association of Bcl-2 expression is prostate tumors with progression to androgen independence is an observation, not a cause and effect. This assertion is acknowledged, but this reference has not been relied upon for showing a cause and effect, as stated in the rejection, Bcl-2 expression in prostate tumors is associated with progression to androgen independence.

Applicants additionally argue no explanation has been provided why the limitation of claim 8, that the antisense overlaps with the translation initiation or termination site, is taught or suggested by the cited references. Translation initiation and termination sites are known preferred target regions for antisense oligonucleotides as evidenced by the

Monia and Baracchini references. The rejection has been clarified to particularly point out these teachings.

Allowable Subject Matter

Claims 9, 11, 29, 30, 33-35, 37, 41 and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
November 26, 2007